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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,146	10/15/2001	Shlomo Melmed	18810-81351	4097

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,146	MELMED ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,25-30 and 36-64* is/are pending in the application.

4a) Of the above claim(s) *39-41 and 62-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,25-30,36-38 and 42-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 10-24-03 has been entered. Claims 21-24 and 31-35 have been canceled. Claims 8 and 36 have been amended. Claims 37-64 have been added. Claims 1-20, 25-30 and 36-64 are pending and claims 1-20, 25-30, 36-38 and 42-61 are under consideration.

Applicants argue that claims 39-41 are directed to non-elected invention but since claims 1, 27-30 and 37, which are linking claims, are allowable, the non-elected groups III, IV and V need to be rejoined for examination (amendment, p. 13). This is not found persuasive because claims 1, 27-30 and 37 are no allowable, therefore, the non-elected groups III, IV and V will not be examined. Claims 62-64 are also drawn to non-elected invention and will not be examined. Thus, claims 39-41 and 62-64 are withdrawn from consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-20, 25-30 and 36 remain rejected and claims 37, 38 and 42-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of a null mutant mouse having null mutation on both pituitary tumor transforming gene (PTTG) alleles in the germ cells and having the phenotypes as disclosed in the specification, such as hyperglycemia, hypoinsulinaemia, and diabetes etc., does not reasonably provide enablement for production of any null mutant rodent

having null mutation on one or both PTTG alleles other than the disclosed null mutant mice set forth above, and the use of said null mutant rodent in the study of mammalian physiology at the cellular, tissue, or organismal level, such as study of diabetes, hyperglycemia, hypoinsulinaemia, and hypoleptinemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 4-23-03 (paper No. 8). Applicant's arguments filed 10-24-03 have been fully considered but they are not persuasive.

Claims 37, 38 and 42-61 are newly added claims. Claims 37 and 38 are directed to a method for studying mammalian physiology, such as diabetes and hyperglycemia etc., at the cellular level, tissue level, organismal level or any combination thereof by using the null mutant rodent comprising in its germ cells an artificially induced PTTG null mutation. Claims 42-61 are directed to a null mutant **mouse** comprising in its germ cells one or two artificially induced PTTG null mutation via homologous recombination with a targeting vector containing a selectable marker, wherein no functional PTTG protein is expressed in somatic cells or germ cells, and the use of said null mutant rodent in the study of mammalian physiology at the cellular, tissue, or organismal level, such as study of diabetes, hyperglycemia, hypoinsulinaemia, and hypoleptinemia.

Applicants argue that the specification teaches how to make and isolate heterozygous PTTG +/- mutant mice and the lack of phenotype description of PTTG +/- null mutants does not negate enablement of producing the mutant mice. Applicants further argue that the specification provides phenotype of PTTG -/- mutant mice so that

one skilled in the art would know how to conduct phenotypic screening of PTTG +/- mutants (amendment, p. 14, 15). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-03 (paper No. 8). As discussed in the preceding Official action, the phenotype of a transgenic knockout organism was unpredictable at the time of filing. Variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals and genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype. The phenotype resulting from a null mutation can depend on the general genetic background of mouse strains used. Further, it was known in the art that it is not uncommon for heterozygous mutant animals to be indistinguishable from wild type animals since a dominant protein expressed by one allele can compensate the loss of another allele. Therefore, although methods of making and screening heterozygous mutant rodent or mice are known, the phenotypes of the heterozygous mutant rodent or mice are still unpredictable at the time of the invention. Since no phenotypes of the claimed heterozygous mutant rodent or mice have been disclosed, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that experimentation is permissible and is not bar to enablement, and the specification teaches how to make and screen PTTG null mutant. Applicants further argue that there are known methods to screen the problems that contribute to phenotypic differences (amendment, p. 15-17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-03 (paper No. 8) and the reasons set forth above. The phenotype of a transgenic knockout organism was

unpredictable at the time of filing. Variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals and genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype. Although methods of making and screening PTTG mutant rodent or mice are known, the phenotypes of the PTTG mutant rodent or mice are still unpredictable at the time of the invention. Since the resulting phenotypes of PTTG mutant rodent or mice via various knockout strategies were unpredictable at the time of the invention, the trial and error experimentation to determine said phenotypes are not routine experimentations and would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Applicants cite references Asamoto et al. regarding the preparation of transgenic rats carrying human c-Ha-ras oncogene and screening for two transgenic rats out of 211 potential transgenic rats by PCR and southern blot screening (amendment, p. 17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-03 (paper No. 8) and the reasons set forth above. The claims do not specify the phenotype of the PTTG mutant rodent or mice except claims 27 and 55 (claim 27 encompasses any PTTG mutant rodent and claim 55 encompasses heterozygous PTTG mutant mice), therefore, the claims encompass PTTG null mutants having any phenotype. Further, rodent includes mice, squirrels, rats, hamsters, beavers, woodchucks, gophers, voles, marmots, guinea pigs, and agoutas etc. Since the resulting phenotypes of PTTG mutant rodent or mice via various knockout strategies were unpredictable at the time of the invention, the trial and error experimentation to determine said phenotypes are not

routine experimentations and would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the cited references Houdebine and Seamark are too old and these references disclose using male and female germ cells, rather than ES cells, to generate transgenic animals (Houdebine, Table 6 and Seamark, p. 653-657), and the specification discloses using oocytes and male germ cells to make transgenic animal. Applicants further cite references Thorsell et al., Smith et al., Reid et al., and Sato et al., regarding preparation of transgenic rats using methods other than ES cells, such as microinjection (amendment, p. 18-19). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-03 (paper No. 8) and the reasons set forth above. The cited references regarding the availability of the ES cells are concerning claims 7-10 that require the use of ES cells for producing the claimed PTTG mutant rodent. Rodent includes mice, squirrels, rats, hamsters, beavers, woodchucks, gophers, voles, marmots, guinea pigs, and agoutas etc. Table 6 of Houdebine only provides a list of transgenic animals expressing protein in the milk but does not indicate using ES cells to make those transgenic animals. Seamark points out that even pig's pluripotent ES cells can be created, no group has demonstrated totipotency of these cells through reinstating their genome within a germ line, and procedures for reinstating the ES cell genome into a germ line are still far from routine. The references cited by applicants all use microinjection to produce transgenic animals. Thus, although the cited Houdebine and Seamark references are not very recent to the filing date of the present invention, i.e. 10-15-01, it is evident that the ES cells available for making transgenic animals at the time of the invention are still very limited and whether the totipotency of these cells can

be reinstated through their genome within a germ line remain to be seen. The specification fails to provide sufficient enabling disclosure for making various PTTG mutant rodents via the use of various rodent ES cells. Thus, claims 1-20, 25-30 and 36 remain rejected and claims 37, 38 and 42-61 are rejected under 35 U.S.C. 112 first paragraph.

Conclusion

No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. Due to the move of USPTO to new site in Alexandria, Virginia, examiner's

telephone number will be changed to (571) 272-0726 **after January 12, 2004**. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.